Predictive Capability of an HIV Model Calibrated with Treatment Interruption Data

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work performed at

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in collaboration with
H.T. Banks, Marie Davidian, and Eric S. Rosenberg

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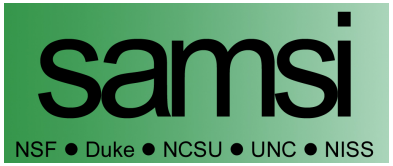


Outline: HIV Model Calibration and Prediction

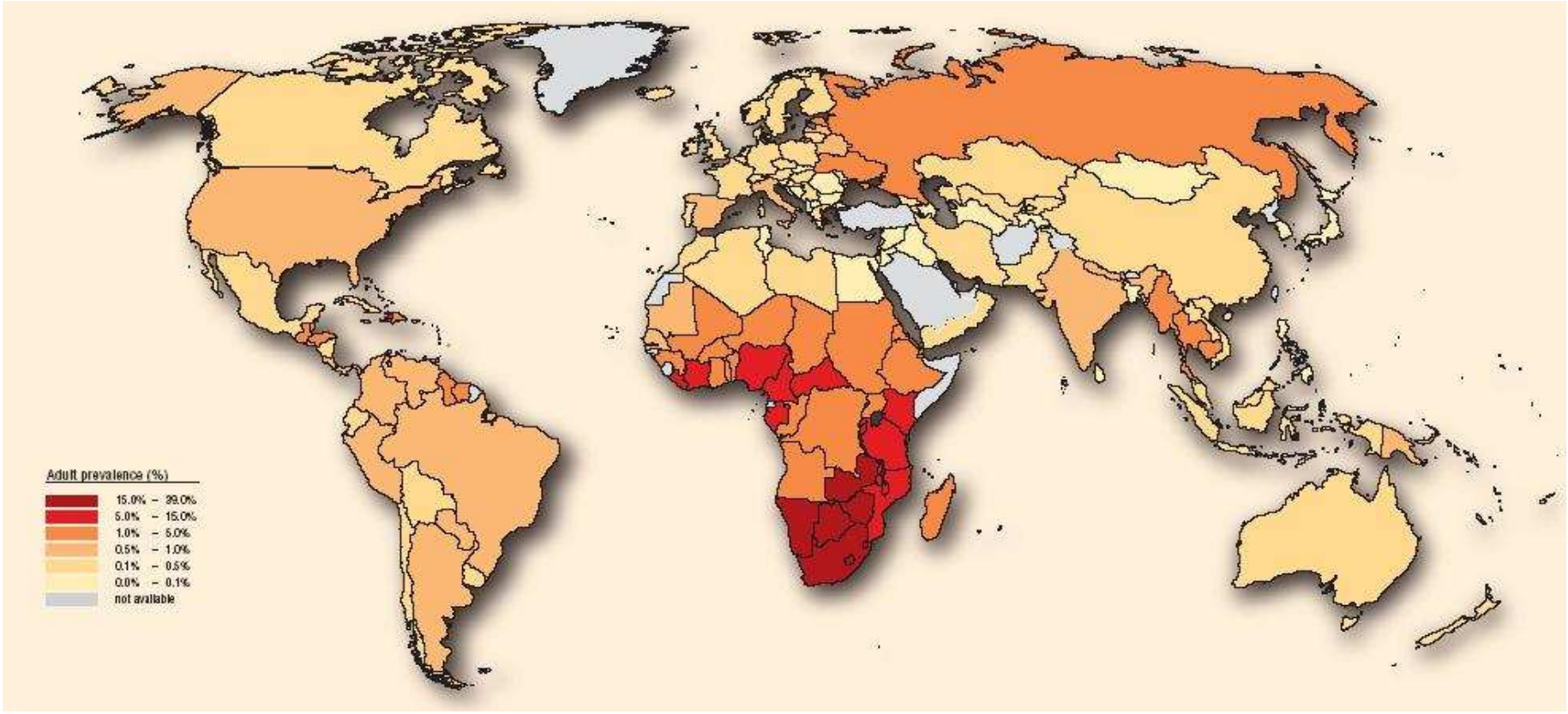
Goal: *Employ patient data to calibrate a model of in-host HIV infection and use it to predict long-term patient behavior.*

1. HIV infection and structured treatment interruptions (STIs)
2. Overview of available clinical data
3. Nonlinear ordinary differential equation model for in-host viral and immune system dynamics
4. Inverse problem for model calibration with censored data
5. Results with calibrated model
6. Conclusions

B.M. Adams, H.T. Banks, M. Davidian, and E.S. Rosenberg, *Estimation and Prediction with HIV Treatment Interruption Data*, Bulletin of Mathematical Biology, *accepted pending minor revisions*.

Worldwide Adult HIV Prevalence

38 million infected as of 2003 (WHO/UNAIDS)



HIV and Treatment

- Human Immunodeficiency Virus is a retrovirus.
- Infects CD4 helper **T-cells** of the **immune system** to reproduce
- Typical HIV treatment (combination therapy) **suppresses viral infection and production**.

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Structured Treatment Interruptions (STIs)

- **Drug holidays** – alternative to continuous therapy
- Break from serious side effects, reduced drug treatment cost
- Could **boost immune system**, cause self-vaccination (Berlin patient)
- May effect reversion from drug resistant to wild type virus

Data from Clinical Acute Infection Study

- Eric Rosenberg, M.D., Mass. General Hospital, Boston, tracks over 120 patients in **acute and early infection** phases
- Early phases believed important for establishing immune responses
- **Measures** T-cell counts, viral load, immune responses
- Some on STI: control drug via fixed schedule or feedback

treatment protocol

(control input $\epsilon(t)$:

drug efficacy)

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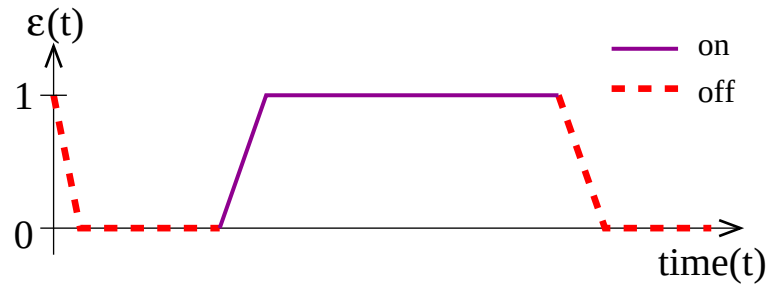
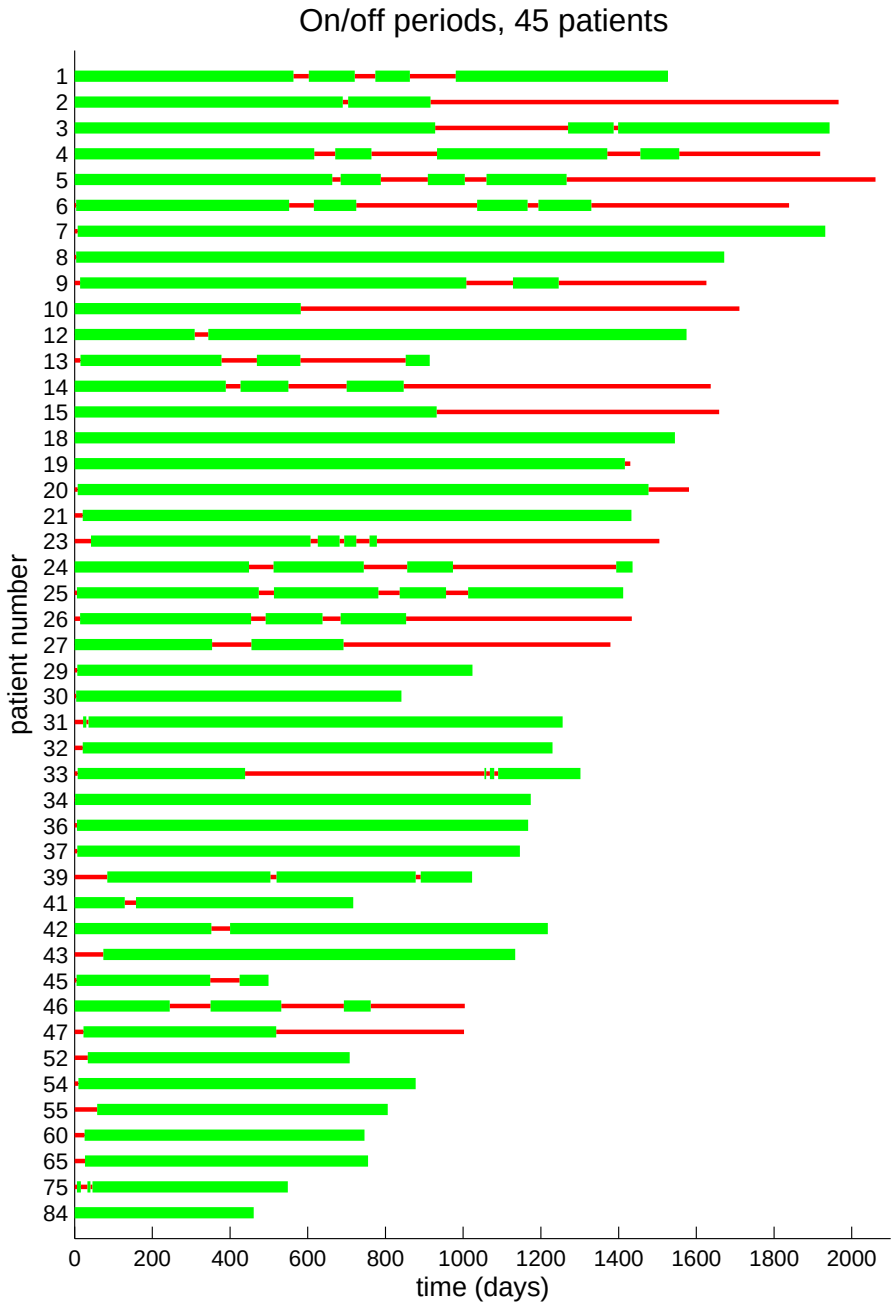


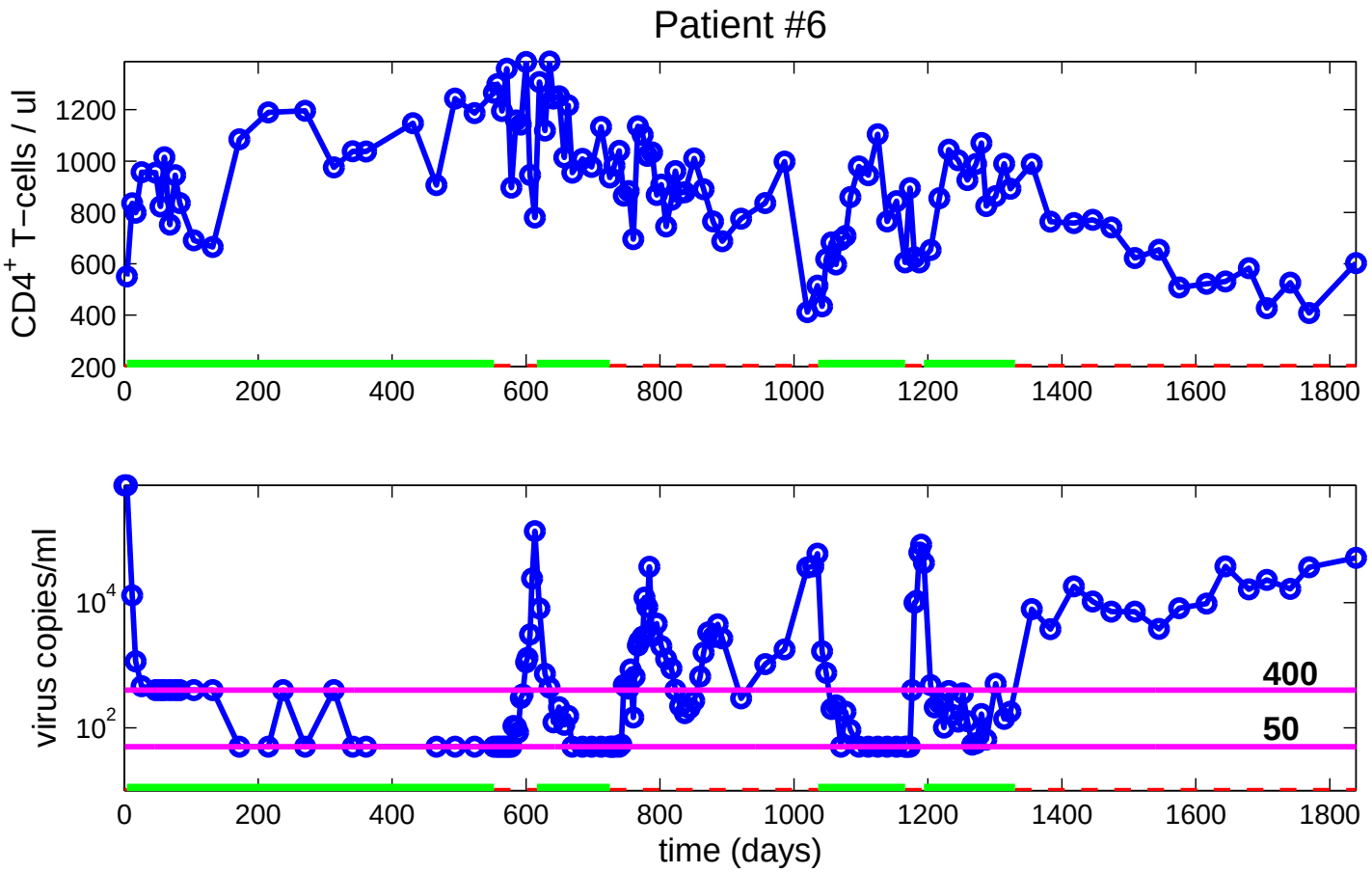
Can we use model to predict clinical data and differentiate between various patient outcomes?

Interruption Patterns

- 45 patients
- 10 or more of each CD4 T-cell, viral load measurements in first half of logitudinal data
- 16 spend 30–70% time off treatment



Typical Study Data



- **Red bar** denotes off treatment periods – note viral rebound
- Viral load measurements have limit of detection: 400 or 50 copies/ml (censoring)

Overview: Modeling and Control for HIV

GOAL: Use HIV infection models to help Rosenberg understand patient data (e.g, what differentiates rapid progressors from long-term non-progressors) and suggest better treatment schemes.

Survey Paper: JCAM special issue on Mathematics Applied to Immunology (2005)

- Surveyed, selected, and integrated models, performed calibration
- Advised control theory collaborators on using model to determine optimal treatment schedules (MBE **1** (2004), 223–241)
- Chose patient data to fit based on analysis with POD (SVD, PCA)
- **Developed and applied mathematical and statistical inverse problem methods to fit model to patient data**, including nonparametric techniques to determine distribution of model parameters across population. (Ph.D. dissertation)
- Ongoing NCSU efforts to develop more detailed immune system models.

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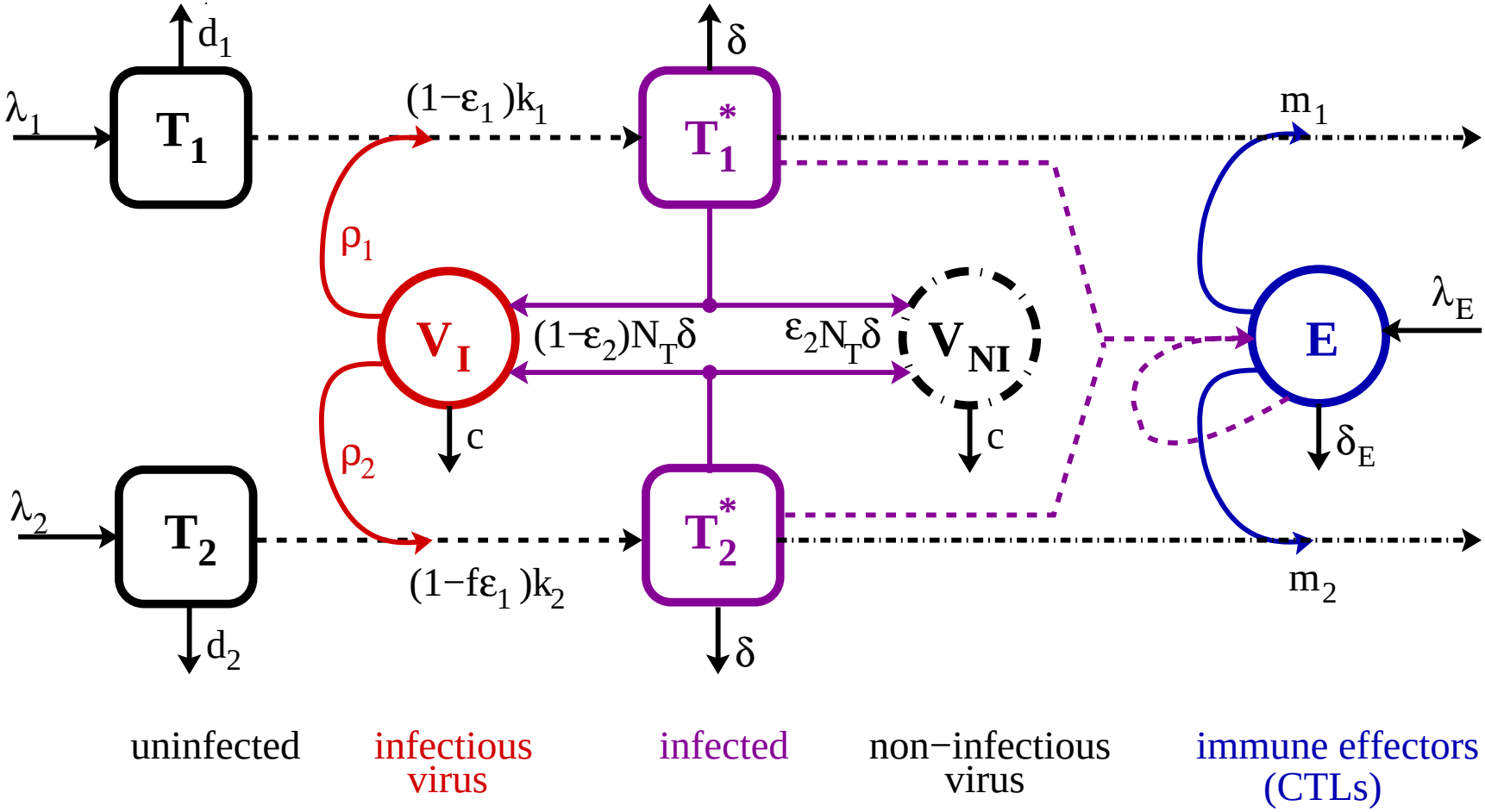
HIV Infection Dynamics Model

- Based on Callaway–Perelson (2001), Bonhoeffer, et. al. (2000) models
- Two co-circulating target cell populations T_1, T_2



HIV Infection Dynamics Model

Uninfected type 1: $$\dot{\mathbf{T}}_\mathbf{1} = \lambda_1 - d_1\mathbf{T_1} - (1-\epsilon_1)k_1\mathbf{V_I}\mathbf{T_1}$$

Uninfected type 2: $$\dot{\mathbf{T}}_\mathbf{2} = \lambda_2 - d_2\mathbf{T_2} - (1-f\epsilon_1)k_2\mathbf{V_I}\mathbf{T_2}$$

Infected type 1: $$\dot{\mathbf{T}}_\mathbf{1}^* = (1-\epsilon_1)k_1\mathbf{V_I}\mathbf{T_1} - \delta\mathbf{T}_\mathbf{1}^* - m_1\mathbf{E}\mathbf{T}_\mathbf{1}^*$$

Infected type 2: $$\dot{\mathbf{T}}_\mathbf{2}^* = (1-f\epsilon_1)k_2\mathbf{V_I}\mathbf{T_2} - \delta\mathbf{T}_\mathbf{2}^* - m_2\mathbf{E}\mathbf{T}_\mathbf{2}^*$$

Infectious virus: $$\dot{\mathbf{V}}_\mathbf{I} = (1-\epsilon_2)N_T\delta(\mathbf{T}_\mathbf{1}^* + \mathbf{T}_\mathbf{2}^*) - c\mathbf{V_I} - [(1-\epsilon_1)\rho_1 k_1\mathbf{T_1} + (1-f\epsilon_1)\rho_2 k_2\mathbf{T_2}]\,\mathbf{V_I}$$

Non-infect. virus: $$\dot{\mathbf{V}}_\mathbf{NI} = \epsilon_2 N_T\delta(\mathbf{T}_\mathbf{1}^* + \mathbf{T}_\mathbf{2}^*) - c\mathbf{V_{NI}}$$

Immune effectors: $$\dot{\mathbf{E}} = \lambda_E + \frac{b_E(\mathbf{T}_\mathbf{1}^*+\mathbf{T}_\mathbf{2}^*)}{(\mathbf{T}_\mathbf{1}^*+\mathbf{T}_\mathbf{2}^*)+K_b}\mathbf{E} - \frac{d_E(\mathbf{T}_\mathbf{1}^*+\mathbf{T}_\mathbf{2}^*)}{(\mathbf{T}_\mathbf{1}^*+\mathbf{T}_\mathbf{2}^*)+K_d}\mathbf{E} - \delta_E\mathbf{E}$$

- q will denote one or more model parameters (of interest), e.g., $q = [k_1, c, N_T]$ and $\mathbf{z}$ the observed states $\mathbf{z} = [z_1, z_2] = \log_{10}[\mathbf{T_1} + \mathbf{T}_\mathbf{1}^*, \mathbf{V_I} + \mathbf{V_{NI}}]$.

Helpful Model Features

- Incorporates single or multi-drug therapy with **realistic sensitivity**
- Predicts low, **non-zero viral load** equilibrium under therapy (hence rebound)
- Multiple off-treatment stable steady states; **can determine drug control to drive between states via treatment interruptions**

	EQ_1	EQ_2	EQ_3
$\mathbf{T_1}$ (cells/ml)	1000000	163573	967839
$\mathbf{T_2}$ (cells/ml)	3198	5	621
$\mathbf{T_1^*}$ (cells/ml)	0	11945	76
$\mathbf{T_2^*}$ (cells/ml)	0	46	6
$\mathbf{V}$ (copies/ml)	0	63919	415
$\mathbf{E}$ (cells/ml)	10	24	353108
local stability	unstable	stable	stable
	uninfected	*viral dominant*	*immune dominant*

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Single Patient Inverse Problems

- **Data:** for each patient $j = 1 \ldots N_P$, we have log-scaled data pairs $(t^{ij}, \mathbf{y}^{ij})$ at times $t^{ij}, i = 1, \ldots, N_j$.
- **Math. Model:** (log-scaled) components of ODE solution: $\mathbf{z}(t^{ij}; q)$
- **Stat. Model** Assume error model for observations, e.g., $y_s^{ij} = z_s(t^{ij}; q^0) + e^{ij}$ where $e^{ij} \sim \mathcal{N}(0, \sigma^2)$.

  (for assay data: variance typically proportional to square of load)

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  (for assay data: variance typically proportional to square of load)

Fit ODE model to **each patient** j yielding parameters $\mathbf{q}_j$:

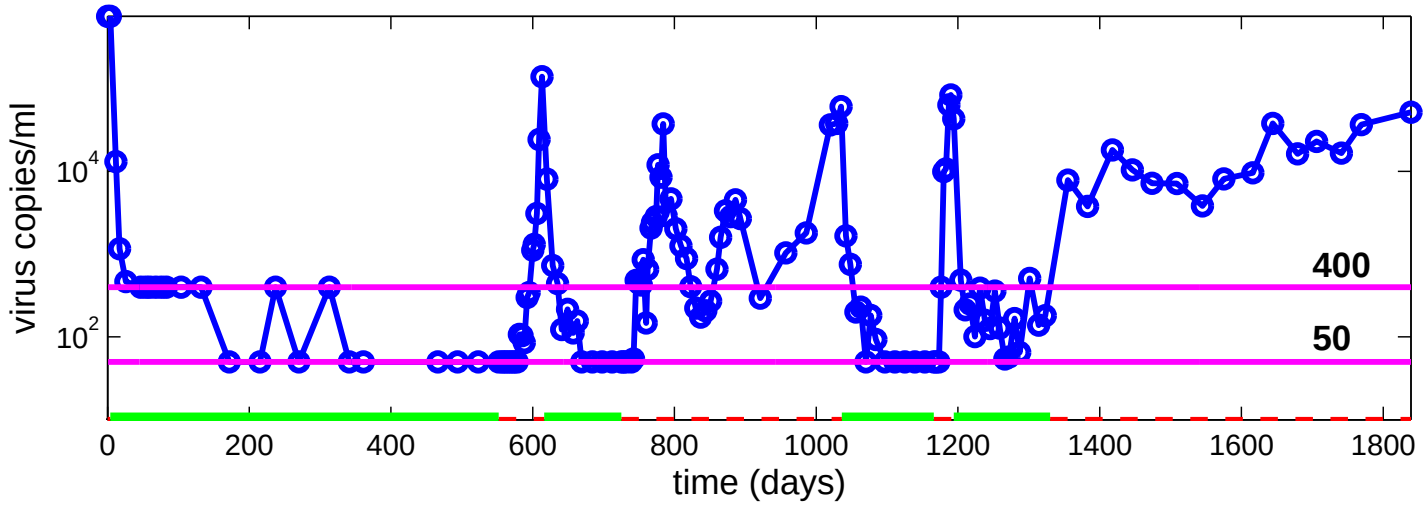
$$q_j^* = \arg\min_{q \in Q} J(q) = \frac{1}{N_j} \sum_{i=1}^{N_j} \left| \mathbf{z}(t^{ij}; q) - \mathbf{y}^{ij} \right|^2$$

(standard nonlinear least squares), then perform statistical analysis.

Problem with Standard NLSQ Approach

$$q_j^* = \arg\min_{q \in Q} J(q) = \frac{1}{N_j} \sum_{i=1}^{N_j} \left| \mathbf{z}(t^{ij}; q) - \mathbf{y}^{ij} \right|^2$$

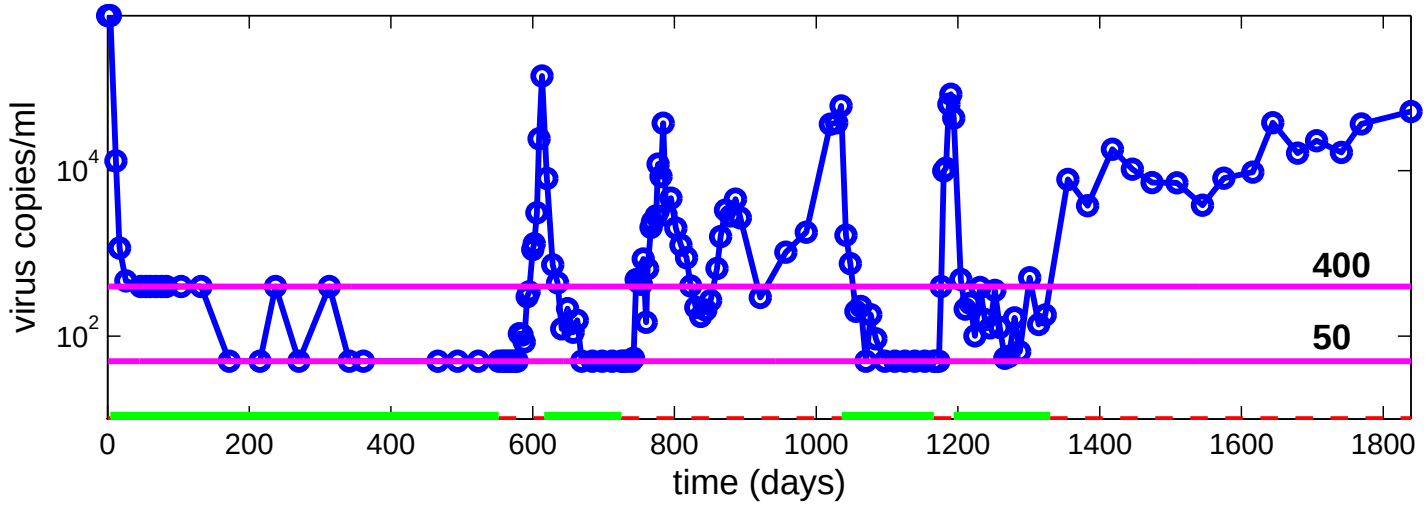
- Recall viral load measurements have **lower limit of quantification**: $L = 400$ or 50 copies/ml
- Need to **quantify uncertainty** about censored data, leveraging knowledge that they are below detection limit (in $[0, L]$)



Censored Data Approach

IDEA: When data are censored, make a probability statement about their values.

- Still assume viral load V data y_2^{ij} arise from model $z_2^{ij}(q)$, but when below the limit of detection, assume $\log$ data follow **truncated** normal distribution.
- χ^i *will indicate censored measurements* $(\chi^i_{(y^i<L)} = 0)$ *and uncensored* $(\chi^i_{(y^i \geq L)} = 1)$.



Individual Patient Estimates: Censored Data Method

1. Perform **initial least squares fit** to data to obtain q^* and an estimate of variance $\hat{\sigma}^2$.

2. **Replace censored data points** using best knowledge of distribution $y_2^{ij} \sim \mathcal{N}(z^{ij}(q^*), \hat{\sigma}^2)$:

$$\tilde{y}_2^{ij} = \chi^i y_2^{ij} + (1 - \chi^i) E[y_2^{ij} | y_2^{ij} < L]$$

3. Minimize least squares criterion **using modified data**

$$q^* = \arg\min_{q \in Q} J(q) = \frac{1}{N_j} \sum_{i=1}^{N_j} \left| \mathbf{z}(t^{ij}; q) - \tilde{\mathbf{y}}^{ij} \right|^2$$

   to update q^*, $\hat{\sigma}^2$. Return to 2., iterate to convergence.

Approach based on EM algorithm for maximum likelihood. Solve nonlinear least squares problem with `DIRECT` *(D.E. Finkel) and* `lsqnonlin` *(Matlab).*

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Model Calibration and Prediction

GOAL: Evaluate model's predictive ability by fitting to half of each patient's longitudinal data, then attempt to predict full time series.

1. Emulate "book" parameters by estimating all model parameters and initial conditions for each of 45 patients and averaging.

2. Fix less sensitive model parameters at book values

3. Estimate most sensitive 8 parameters and 3 initial conditions for each patient using:

   (a) half of the available longitudinal data

   (b) all of the available longitudinal data

4. Simulate model with each parameter set (a) and (b); compare to each other and to full data series.

Model Parameters estimated vs. fixed at average

Uninfected type 1 (T_1^0):
$$\dot{T}_1 = \lambda_1 - d_1 T_1 - (1-\epsilon_1) k_1 V_I T_1$$

Uninfected type 2 (T_2^0):
$$\dot{T}_2 = \lambda_2 - d_2 T_2 - (1-f\epsilon_1) k_2 V_I T_2$$

Infected type 1 (T_1^{*0}):
$$\dot{T}_1^* = (1-\epsilon_1) k_1 V_I T_1 - \delta T_1^* - m_1 E T_1^*$$

Infected type 2 (T_2^{*0}):
$$\dot{T}_2^* = (1-f\epsilon_1) k_2 V_I T_2 - \delta T_2^* - m_2 E T_2^*$$

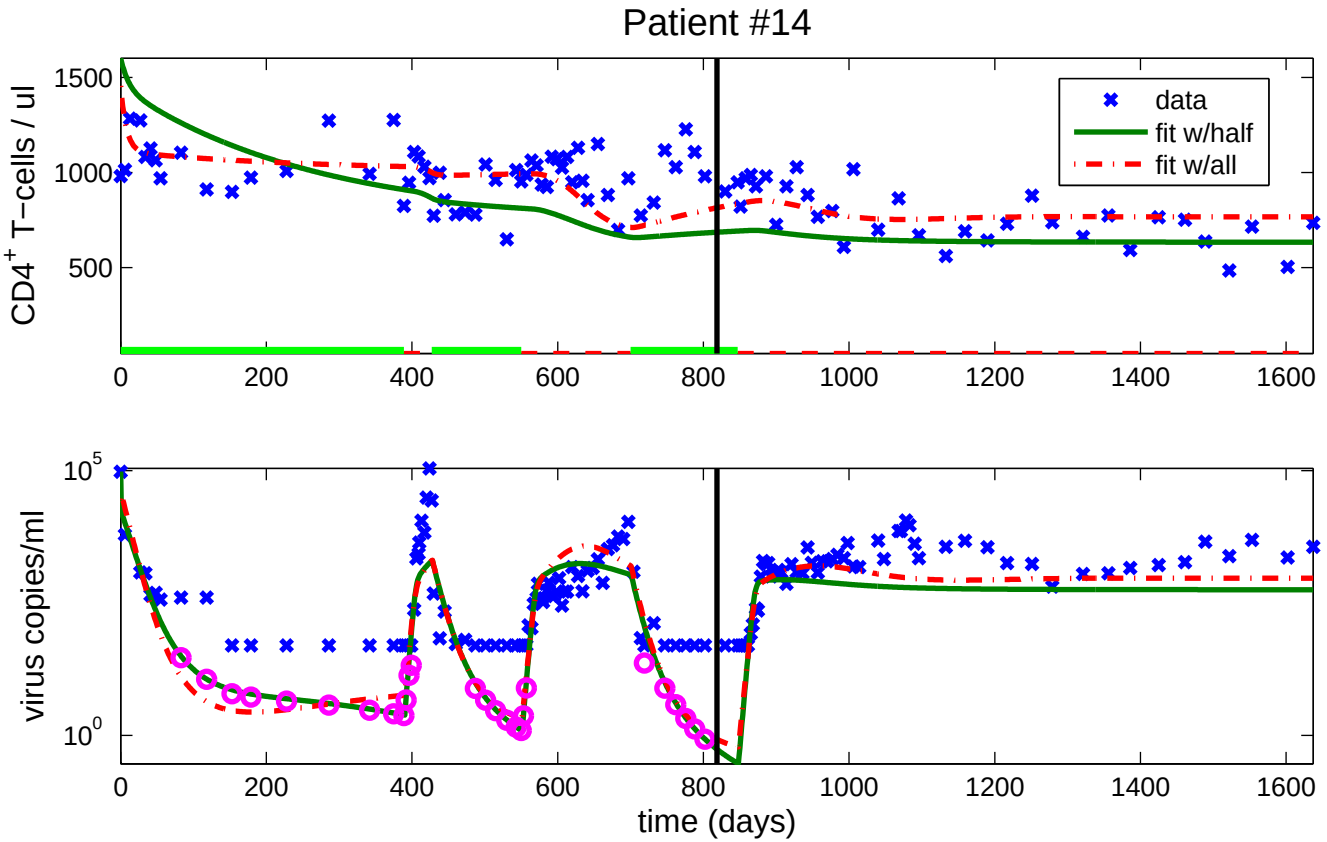
Infectious virus (V_I^0):
$$\dot{V}_I = (1-\epsilon_2) N_T \delta (T_1^* + T_2^*) - c V_I - [(1-\epsilon_1)\rho_1 k_1 T_1 + (1-f\epsilon_1)\rho_2 k_2 T_2] V_I$$

Non-infect. virus (V_{NI}^0):
$$\dot{V}_{NI} = \epsilon_2 N_T \delta (T_1^* + T_2^*) - c V_{NI}$$

Immune effectors (E^0):
$$\dot{E} = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E$$

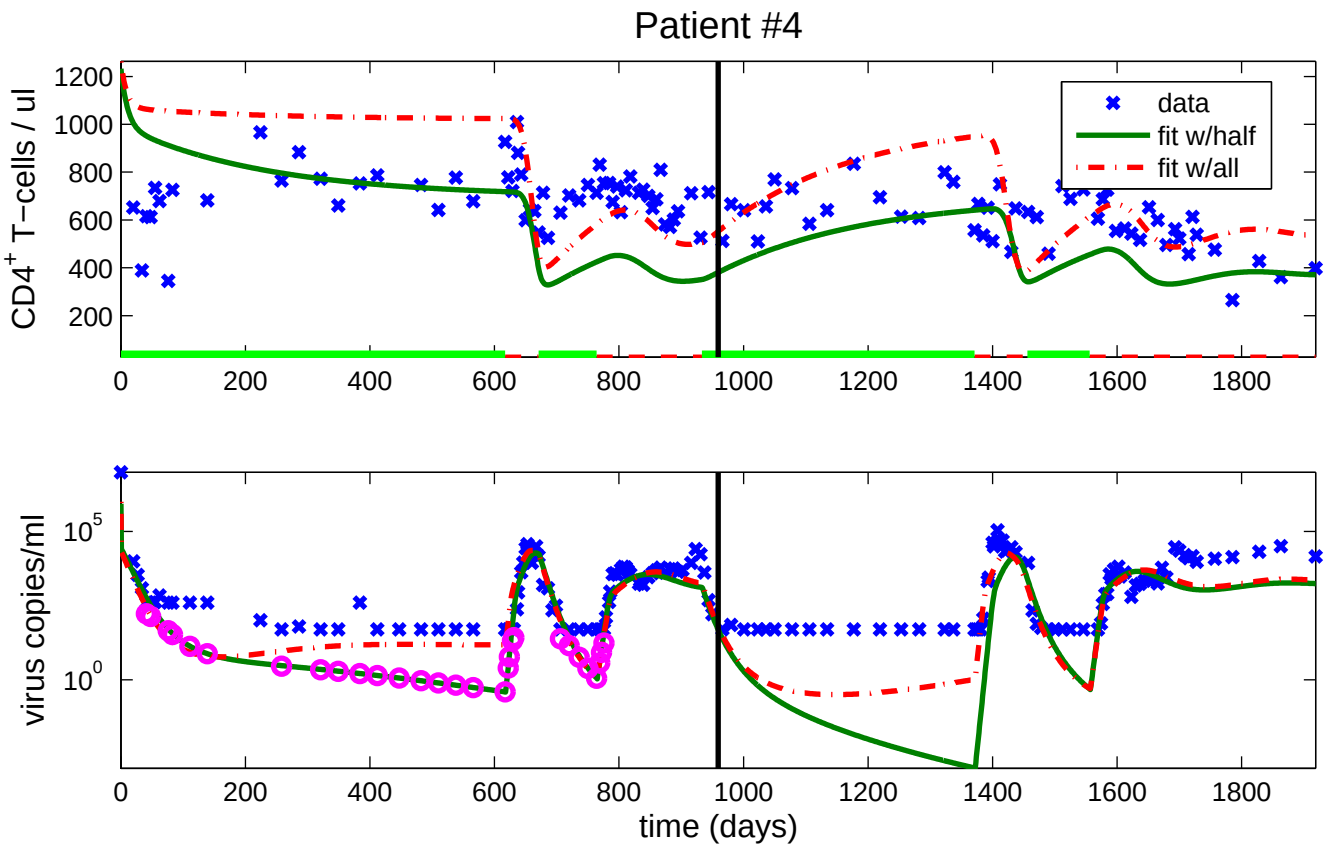
λ_2	1.0099e-01	δ	1.8651e-01	T_2^0	1.7545e+01
d_2	2.2109e-02	m_1	2.4385e-02	T_2^{*0}	6.0955e-01
f	5.3915e-01	m_2	1.3099e-02	V_{NI}^0	4.9909e+03
k_2	5.5290e-04	b_E	1.6136e-01	E^0	1.8834e-01

Model Fit: Two Early Interruptions



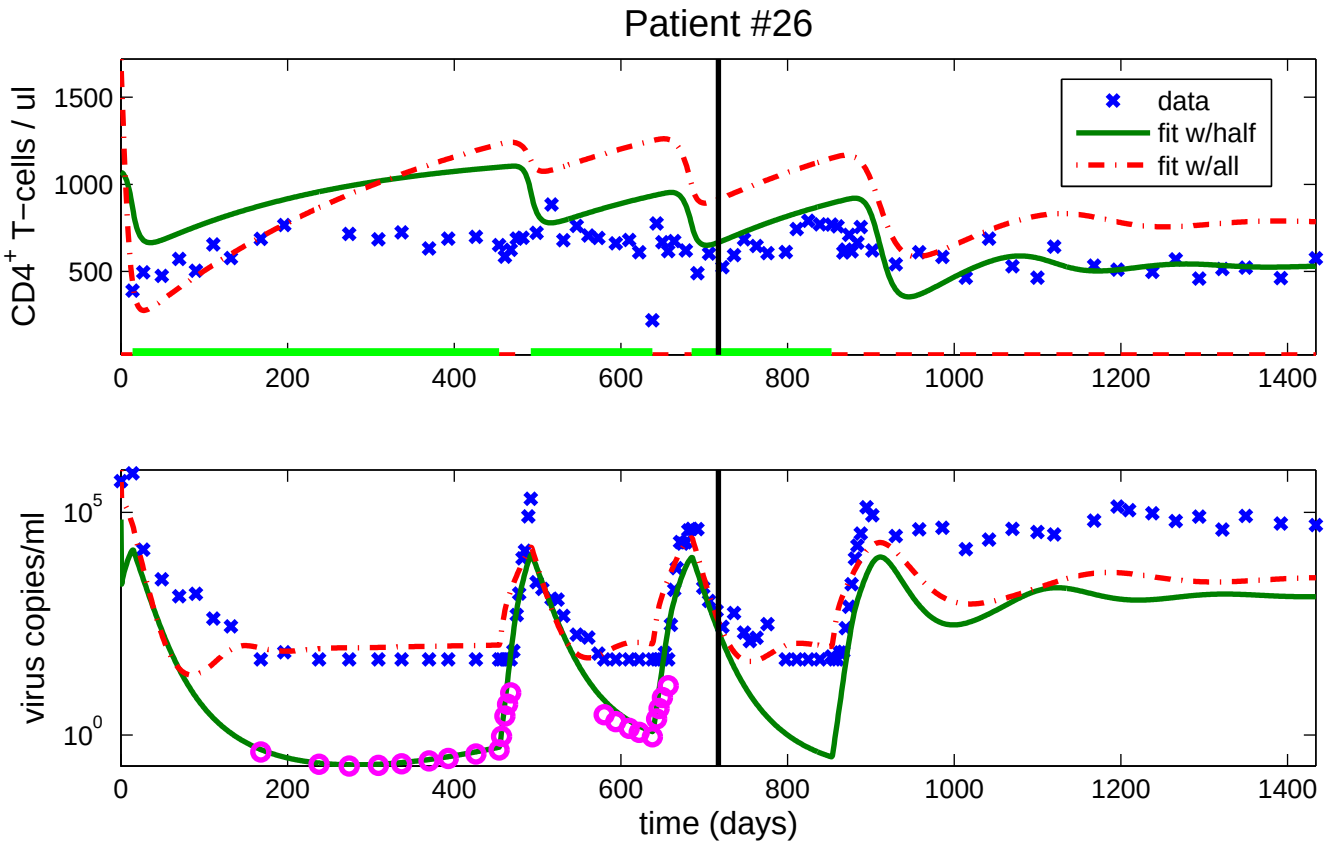
- Good agreement between half and full data set calibrations, and to data
- Reasonable prediction of long-term off treatment period
- Capture viral peaks? Capture T-cell trend? (T-cell data very noisy)

Model Fit: Two Early Interruptions



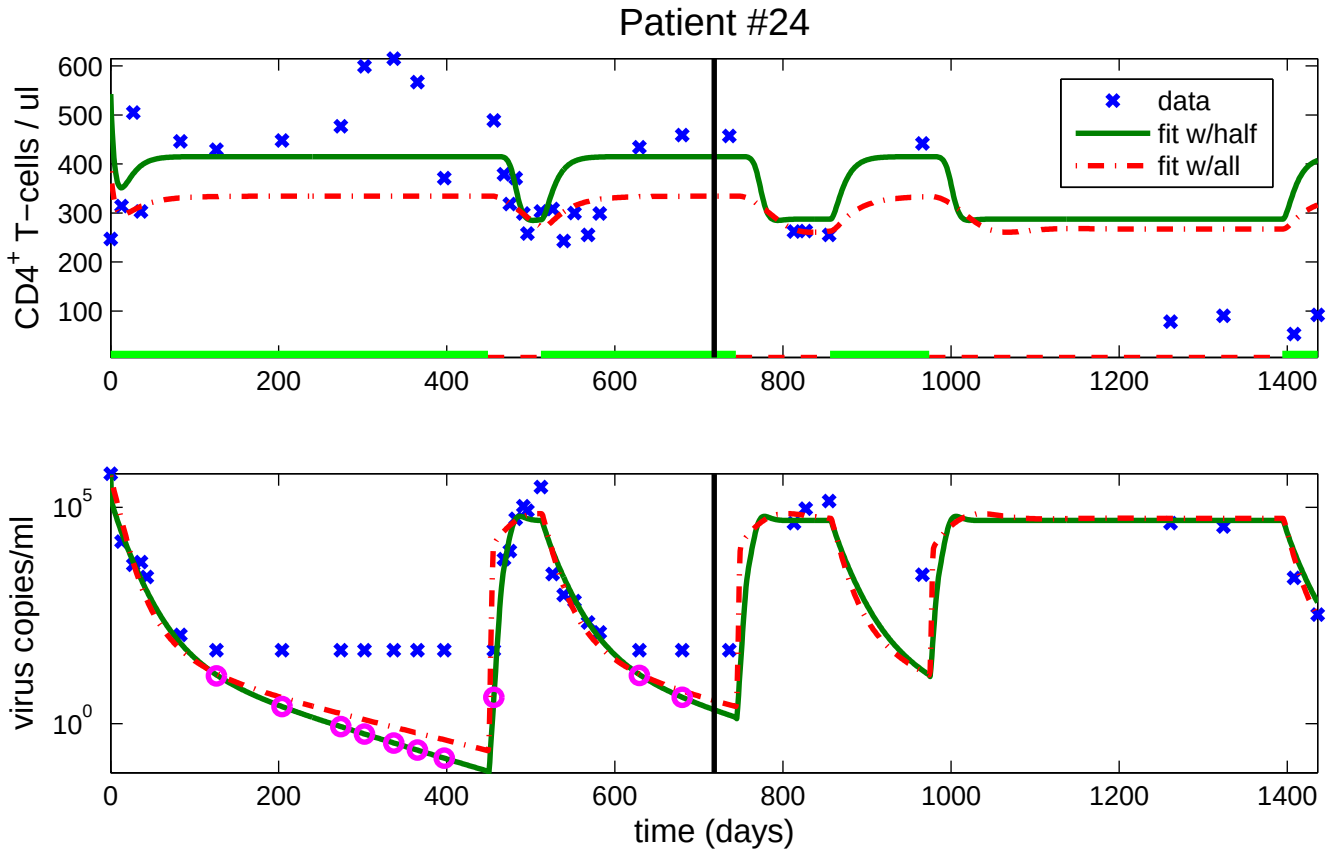
- Better fit to viral peaks
- Reasonable steady state prediction (within 1 log)
- T-cell fit may be improved by (variance) weighted least squares

Poor Model Fit: Two Early Interruptions



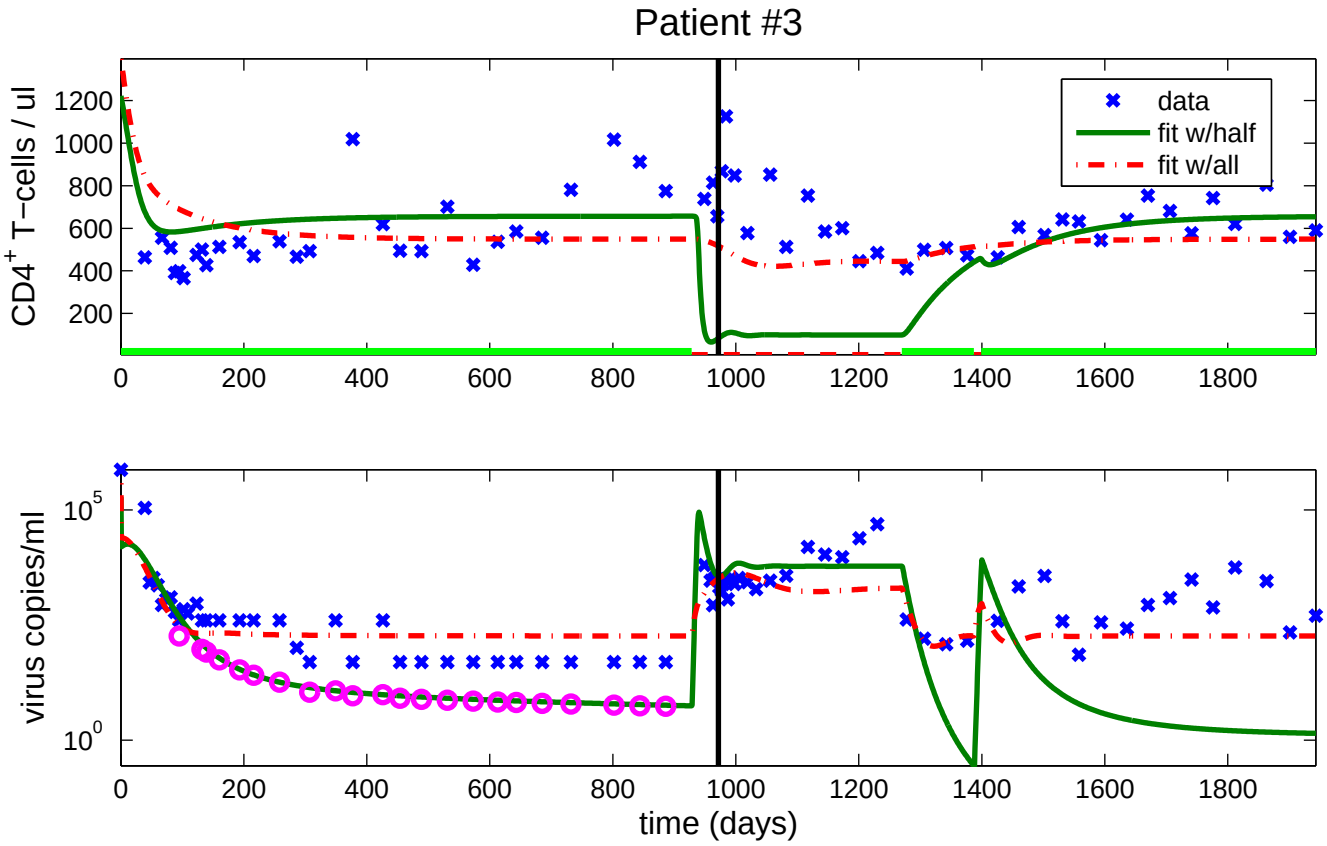
- Despite fitting early viral peaks, do not predict steady state well
- Even full data may be challenging to fit (local minimum?)

Model Fit: One Early Interruption



- Single interruption can yield reasonable viral load predictions
- Suggests need for better T-cell dynamics model (note low T-cell count), though some T-cell transients are modeled.

Model Fit: No Early Interruptions



- With no early interruption, it is difficult (impossible?) to predict later interruption.
- Noticable difference between fits with half and full datasets

  (e.g., N_T=1.829e+01 vs. 3.677e+01)

Conclusions and Research Needs

- HIV model with immune response can predict small viral loads during suppression and viral rebound during treatment interruption
- Censored data algorithm offers a means to quantify uncertainty when measurements are below assay limits
- Calibrated model capable of predicting long-term patient behavior; need means to quantify success of prediction (LSQ error? early peak fit? steady state?)
- Need better quantification of T-cell measurement error and modeling transients (moving average?)
- Relevant immune responses need to be quantitatively characterized and modeled (in progress at NCSU)

Thank You!

Brian M. Adams

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(optimization, uncertainty quantification, MEMS design, epidemic modeling)

Collaborators

- H.T. Banks, S.L. Grove, S. Hu, G.M. Kepler, H. Kwon, H.T. Tran, S.N. Wynne (mathematics); M. Davidian, S. Ghosh, Y. Ma (statistics); E.S. Rosenberg (clinical, MGH Boston)

Publications

- B.M. Adams, H.T. Banks, M. Davidian, and E.S. Rosenberg, Estimation and Prediction with HIV Treatment Interruption Data, (results for all patients) *CRSC Tech. Rpt. CRSC-TR05-40,* NC State University, October 2005; *Bulletin of Mathematical Biology,* accepted pending minor revisions.
- B.M. Adams, H.T. Banks, H.T. Tran, and H. Kwon, Dynamic Multidrug Therapies for HIV: Optimal and STI Control Approaches, *CRSC Tech. Rpt. CRSC-TR04-18,* NC State University, April 2004; *Mathematical Biosciences and Engineering* 1 (2004), 223-241.
- B.M. Adams, H.T. Banks, M. Davidian, et. al., HIV Dynamics: Modeling, Data Analysis, and Optimal Treatment Protocols, *CRSC Tech. Rpt. CRSC-TR04-05,* NC State University, February 2004; *Journal of Computational and Applied Mathematics* (2005).